prior art situation in view of the pending claims.

The allowed claims correspond as follows to the new claims: claim 19 reciting cytolytic or cytotoxic alone, systemic, and at least 4 x 10^8 PFU/kg corresponds to claims 167 and 283; claim 21 reciting cytolytic or cytotoxic alone, systemic, and at least 4 x 10^9 PFU/kg corresponds to claims 168 and 285; claim 49 reciting cytolytic or cytotoxic alone, systemic, and further a chemotherapeutic or radiotherapeutic agent corresponds to claims 170 and 180.

The claims now all recite that the Newcastle disease virus ("Ndv") is administered in an amount which alone is cytolytic to the cancer. This aspect ("alone is cytolytic") distinguishes the claims from the prior art (Bohle et al., Cancer, 66:1517-1523, 1990; Murray et al., Cancer, 40:680-686, 1977; Cassel et al., Cancer, 52:856-860, 1990) cited under § 102(b) in the previous Office Action. The work described in these prior art references represents an immunologic or vaccine approach, where a Newcastle disease virus is used in combination with tumor cells to activate and direct an immune response against the latter. See, e.g., Schirrmacher et al., Cancer Rev., 5:19-49, 1986 (listed as "A61" in the IDS filed October 25, 1994). There is no suggestion of any cytolytic effect on the cancer due to Ndv alone. In fact, calculations performed by Dr. Lorence, an inventor of the subject matter of the present application, show the amounts of Ndv employed in the prior art experiments on which the rejection is based were far less than would be effective to achieve a cytolytic effect. See, Lorence Declaration, filed June 30, 1995, especially paragraph No. 4. Thus, the prior art rejection is untenable for all claims. In fact, all the prior art fails to disclose any of the claimed subject matter or motivate a skilled worker to modify any prior art work in the manner required to arrive at any of the claimed subject matter.

The claims directed to administering mesogenic Ndv are especially nonobvious. Thus, there is no motivation from the prior art as a whole to use cytolytic amounts of mesogenic Ndv to treat cancer.

For example, there was no reasonable expectation in the prior art that mesogenic Ndv alone would be cytolytic to cancer cells. Shoham et al. (Nat Immun Cell Growth Regul 9:156-172, 1990) employed NDV-Roakin, a mesogenic strain, in a murine Lewis lung carcinoma ("3LL") cultured in a C57B1/6 mouse host but concluded that the Ndv strain was nonlytic and did not cause a cytopathic effect in the 3LL cells. See, e.g., Page

167, beginning at column 1, "Augmentation of Antitumor Immunity by a Nonlytic Virus-Tumor Cell Combination." The mesogenic Ndv worked poorly in retarding tumor growth when administered alone, requiring administration of tumor cells infected with Ndv ("nonlytic virus-tumor cell combination") to achieve a good effect in mice. See, especially Fig. 2 and Page 170, column 2. Thus, there would have been no motivation from Shoham for a skilled worker even to try other non-lytic mesogenic strains in view of the teaching away of such an approach. Certainly, there is nothing in Shoham suggesting the entirely different concept of using a mesogenic strain in an amount which alone is cytolytic to cancer cells.

The same conclusion also applies when further considering the remainder of the prior art. There is no use or suggestion of any lytic mesogenic Ndv strains to treat cancer in mammals.

Schirrmacher et al. (A61), 1986, reports experiments showing that a velogenic (high virulence to chickens) Ndv strain ("Italien") was lytic to human melanoma MeWo-Met tumors growing in Balb/c (nu/nu) mice while a lentogenic (low virulence to chickens) strain ("Ulster") was nonlytic and ineffective when administered under the same conditions. See, e.g., Pages 28-31, especially Fig. 3. Shirrmacher also reports further experiments using "1E10," a less well characterized Ndv derived from the lentogenic Ulster strain. 1E10, a "late lysis" strain having low chicken virulence properties similar to the parent lentogenic Ulster strain (Ahlert and Schirrmacher, Cancer Res., 50:5962-5968, 1990), was much less effective than the velogenic Italien strain in retarding tumor growth. See, especially, Fig. 3.

Claims reciting that the cytolytic amount of Ndv administered results in regression of the cancer, and claims reciting other aspects in combination with regression, are also especially nonobvious. They are at least nonobvious because there was no reasonable expectation that regression could have been achieved by the claimed methods.

Although Csatary (Lancet, 1971) reported regression in three patients upon Ndv administration, this report is anecdotal, lacking the scientific rigor that is necessary for any reasonable teaching to or conclusion by those skilled in the field. For example, Csatary has no controls; no mention of whether additional cancer therapies were given concurrently with the Ndv; small (three) sample size; and insufficient information to repeat the treatment protocols (e.g., Ndv strain, dose, or frequency of administration).

This lack of rigor and detail is reflected in the considerable skepticism which exists among the medical community about the true efficacy of Csatary's treatments. (In a recent [1994] review by Sinkovics and Horvath on the virus therapy of cancer, Csatary's Ndv work is described: "Open clinical trials have recently been conducted in Hungary by repeated ingestion, inhalation, and administration by enema of the MTH-68/N strain of NDV and other live veterinary viruses [Eckhardt, personal commun., 1992]. We have no access to documented or published case histories of this trial. This NDV strain is given to patients without any laboratory documentation of its effects.") Moreover, there is little information in Csatary (or Csatary, USP No. 5,215,745) on which to base even a guess of how any alleged anticancer effect could have been achieved, i.e., cytolytic? immunostimulant? It provides no basis on which a skilled worker could be motivated to modify Csatary's work or that of anyone else.

Cassel and Garrett, Cancer, 11:863-868, 1965, report "extensive sloughening of the pelvic tumor and shrinkage of the supraclavicular lymph node metastasis" following inoculation of Ndv 73-T strain into the tumor. This observation in one patient is also anecdotal, lacking, e.g., controls or reproducibility. The authors, themselves, merely state that their observations are "worthy of more extensive evaluation," without making a definite conclusion about the ability of Ndv 73-T to shrink tumors or providing any basis on which Cassel et al's own work or that of anyone else could be modified. (See also Sinkovics and Horvath, Page 196.)

Thus, neither publication, alone or in combination with anything else, provides any motivation even to try a cytolytic Ndv virus to produce cancer regression in a mammal, let alone any reasonable basis to expect success.

The claims to regression and systemic administration are especially nonobvious since Cassel administered directly into the tumor (as did Reichard et al., J. Surg. Res., 52:448-453, 1992).

In regard to the rejection of claims under § 112, first paragraph, as failing to have support for the term "mesogenic" in the specification as originally filed, applicants refer to their previous response filed March 18, 1996, including a declaration by Dr. Conrad Heilman, Vice-President of Research at Pro-virus, Inc. which is the assignee of the present application. Supplementally, enclosed is a second declaration by Dr. Mark Peeples, a Professor at Rush Medical College, Chicago, Illinois, and an expert in

Newcastle disease virus. Dr. Peeples is a paid consultant to Pro-virus, Inc. In his declaration, he states that one of skill in the art would have necessarily understood that mesogenic strains are specifically included in the methods of treatment described in the patent applications.

Respectfully submitted,

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